AMENDMENTS

In the claims:

Please cancel Claims 30 and 32.

REMARKS

Claims 10, 11, 20, and 31 are pending in the application.

Examiner's Position

In the Office Action dated December 13, 2002, the Examiner made the following rejections:

(1) Claims 10-11, 20, and 31 were rejected under 35 U.S.C. §101 as allegedly not being supported by either a specific or substantial asserted utility or a well-established utility;

(2) Claims 10-11, 20, and 31 were rejected under 35 U.S.C. §112, first paragraph for asserted lack of enablement; and

(3) Claims 30 and newly added 32 were rejected under 35 U.S.C. §112, first paragraph for asserted lack of written description of the genus of polypeptides comprising the sequence of SEQ ID NOS: 4 or 6, or sequences 99% or 90% identical, respectively, thereto.

Applicants traverse each of these rejections as follows.

35 U.S.C. §101 Utility Rejection Should be Withdrawn

The rejection under 35 U.S.C §101 should be withdrawn because the specification does teach a specific, substantial and credible utility for the claimed polypeptides. As disclosed in the specification at least in figures 1-2 and at pages 4-6, the claimed polypeptides are homologous to type II C-type lectin receptors, namely dendritic cell immunoreceptor (DCIR) and mouse macrophage C-type lectin receptor, both of which have well-established utilities.

On page 4 of the Office Action dated 12/13/2002, the Examiner states that "the specification teaches that SEQ ID NO: 4 is a C-type lectin receptor-like polypeptide" however, the specification "does not teach the activity or biological function of SEQ ID NO: 4." Applicants respectfully traverse for the following reasons.

The claimed polypeptide is a type II C-type lectin, which contains the classical CRD domain at the C-terminus (a type II transmembrane orientation) and the requisite amino acids that are known to mediate calcium-dependent carbohydrate binding. The asserted utility is disclosed in the specification as follows: page 4, line 3 to page 5, line 16 teaches that the claimed polypeptide is a member of the type II C-type lectin subfamily of C-type lectins, which has a well-established biological activity; at page 4, lines 3-24 the specification teaches that SEQ ID NO: 4 recited in the claims shares homology with polypeptide(s) that have the carbohydrate recognition domain (CRD) and calcium-binding domain. In addition, the specification teaches that the claimed polypeptide is a type II C-type lectin receptor most similar to the human dendritic cell immunoreceptor (DCIR) (see figure 2 and page 4, lines 12-15 of the specification). DCIR is a well-known type II C-type lectin receptor that is primarily expressed in hematopoietic cell, including monocyte-derived dendritic cells (DCs), and functions in DC maturation and/or differentiation and serves to uptake antigens in immature DCs (Bates *et al., J. Immunol.* 163:1973-1983 (1999)). The percent similarity between the sequence of the claimed polypeptide and the human DCIR is 69%. One of ordinary skill in the art accepts structural homology based on amino acid sequence identity as a credible method of determining the function of a polypeptide. *See* Henikoff *et al., Science* 278:609-614 (1997), and the sequence identity that SEQ ID NO: 4 shares with other members of the family is more than sufficient to predict activity of the polypeptide of SEQ ID NO: 4.

Applicants submitted a ClustalW multiple sequence alignment in Exhibit 2 of the Response to Office Action dated 7/25/2002, in which the polypeptide of SEQ ID NO: 4 was compared to DCIR, providing further evidence that the claimed polypeptide is a type II C-type lectin receptor. The structural features that establish that the claimed polypeptide is a carbohydrate-binding type II C-type lectin are further evidenced in the ClustalW alignment submitted herein as Exhibit A. In the latter alignment, the residues of the CRD are in bold, the PROSITE C-lectin consensus sequence present in the claimed polypeptide as well as in DCIR is

underlined, while the calcium binding residues are indicated by the dots (▪), cysteines involved in intramolecular disulfide bonds are indicated by the asterisks (*), and the mannose/glucose recognition motif is indicated by the pluses (+). The calcium binding site is required for binding of the carbohydrate moiety while the mannose/glucose recognition motif (-EPN-) determines which carbohydrate moieties the lectin receptor will bind. The alignment clearly exemplifies that the polypeptide of the invention contains both the calcium binding residues and the conserved -EPN- motif as well as the single conserved CRD in the C-terminus, typical of a type II C-type lectin with specificity for mannose and glucose moieties (Drickamer and Taylor, *Annu. Rev. Cell Biol.* 9:237 (1993)). The -EPN- motif was known to be specific for binding mannose and glucose at the time the application was filed. Therefore, the -EPN- motif contained in the claimed polypeptide teaches that the type II C-type lectin of the present invention will recognize mannose and glucose-bearing carbohydrates.

The Examiner has taken the position that "assignment of SEQ ID NO: 4 to a particular subfamily does not make apparent the function or specificity of SEQ ID NO: 4 as [...] different type II receptors have different specificities and bind different ligands," citing Akimoto *et al.* (*Prog. Histochem. Cytochem.* 33:1-92 (1998)) and Drickamer (*Curr. Opin. Struct. Biol.* 9:585-590 (1999)). The paper by Akimoto *et al.* speaks to all of the animal lectins and their organization into subfamilies without giving a detailed analysis of individual type II C-type lectins or a discussion of commonalities among those that have similar functions. The paper by Drickamer speaks to commonalities and differences among C-type lectin domains, such as the CRD. C-type lectin receptors that bind carbohydrate ligands contain conserved calcium binding sites within the CRD, whereas those that do not bind carbohydrates do not have the calcium binding sites in the CRD and therefore bind ligand in a calcium-independent manner. For example, the type II antifreeze glycoprotein of sea raven does not retain the calcium binding site in the CRD and does not bind carbohydrates (see p. 587 of Drickamer). As evidenced in the ClustalW alignment (Exhibit 2 of the Response to Office Action dated 7/25/2002), the polypeptide of SEQ ID NO: 4 contains calcium binding sites within the CRD (denoted with dots (▪)) as well as a mannose/glucose binding motif (denoted with pluses (+)). Therefore, the polypeptide of SEQ ID NO: 4 retains the carbohydrate binding capability and can bind mannose and glucose moieties as ligands in a calcium-dependent manner.

Therefore, the polypeptide of the invention has all the relevant characteristics of a type II C-type lectin receptor, which demonstrates that the claimed polypeptide has a specific utility. The specific utility is also substantial because it is well known that cell surface type II C-type lectin receptors bind molecules containing specific carbohydrate moieties and rapidly internalize them for processing which results in antigen presentation to naïve T cells or in activation/maturation of the host cell. For example, the C-type lectin receptors bind antigenic molecules, such as microbial cell-surface glycoproteins and allergens, in order to present these antigens to other immune cells to initiate an immune response or to activate macrophages to initiate an inflammatory response. DCs are a specialized subset of antigen presenting cells that express type II C-type lectin receptors and whose function is antigen capture. After binding and internalizing the antigen, DCs migrate to secondary lymphoid organs where processed antigen is presented to activate naïve T cells to initiate a primary T cell response (Steinman, *Ann. Rev. Immunol.* 9:271 (1991); Banchereau and Steinman, *Nature* 392:245 (1998)). Thus, DC function is mediated by cell surface receptors including type II C-type lectin receptors which are important for the migration of DCs and their interactions with lymphocytes. In addition, DCIR expression is down-regulated by DC maturation signals (*i.e.* CD40 ligand and bacterial LPS) indicating that DCIR plays a role in DC maturation and/or differentiation and serves to uptake antigens in immature DCs (Bates *et al., J. Immunol.* 163:1973-1983 (1999)). Thus, SEQ ID NO:4 is expected to have a similar utility in that it may play a role in DC maturation and serve to uptake antigens.

At the time of filing, it was known in the art that DCIR, to which SEQ ID NO: 4 is 69% homologous, is expressed in monocyte-derived DCs (Bates *et al., J. Immunol.* 163:1973-1983 (1999)). O'Doherty *et al.* (*J. Exp. Med.* 178:1067-1076 (1993)) show that DCs isolated from human blood express CD4 (*i.e.* are CD4+ cells). Furthermore, DCIR is expressed on resting and naïve cells and is down-regulated as the cells mature (Bates *et al.*, 1999 *supra*). Since DCIR and SEQ ID NO: 4 are 69% homologous, one of skill of the art would expect the expression patterns to be similar, which indeed they are in that both DCIR and SEQ ID NO: 4 are expressed on DCs and resting CD4+ cells (See Declaration by W. Funk provided in the Response to Office Action dated 7/25/2002). It is for this reason that Applicants respectfully disagree with the Examiner's assertion that "the teachings in the declaration [Funk Declaration dated 7/25/2002] with respect

to the expression of SEQ ID NO: 4 mRNA in resting CD4+ and CD19+ cells, but not activated CD4+ cells and activated CD19+ cells [...] was not taught in the specification nor would an artisan reading the specification determine without experimentation that the expression pattern of SEQ ID NO: 4 mRNA was that as presented in the declaration."

It was known in the art at the time of filing that DC function is mediated by cell surface receptors such as type II C-type lectin receptors. Antigen uptake is one of the main sources of signals that induce DC maturation and migration from the periphery to lymphoid organs (Clark *et al., Microbes Infect.* 2:257-272 (2000)). Therefore, in order to regulate the migration of DCs and their subsequent interaction with lymphoid cells, it is reasonable to alter the expression or activity of C-type lectin receptors, such as SEQ ID NO: 4, with the soluble portion.

The specification teaches at least at page 43, lines 6-10 that C-type lectin receptors are involved in inflammatory diseases such as asthma. Currie *et al.* (incorporated by reference in the specification at least at page 5, line 30 to page 6, line 2) demonstrate that binding of pollen starch granules to the macrophage C-type lectin receptor induced a rapid up-regulation of inducible nitric oxide synthase mRNA and subsequent release of nitric oxide by alveolar macrophages resulting in bronchial inflammation. Modulation of the recognition of allergenic particles by the C-type lectin receptor can modulate the inflammatory response and can be used as a therapeutic for allergic airway diseases such as asthma.

The specification also teaches that the claimed polypeptide of SEQ ID NO: 4 is 55% homologous to mouse macrophage C-type lectin receptor (see at least figure 1 and page 4, lines 8-12). The human ortholog of the mouse C-type lectin receptor was determined to be expressed on macrophages which use the carbohydrate recognition system of C-type lectin receptors to bind and internalize allergenic particles, such as pollen starch granules (Currie *et al., J. Immunol.* 164:3878-3886 (2000), incorporated by reference in its entirety in the specification at least on page 5, line 30 to page 6, line 2). Binding of the pollen starch granules to alveolar macrophages via type II C-type lectin receptors stimulates the macrophages thereby eliciting an inflammatory pathway typified by significant bronchoconstriction as manifested in allergic airway diseases such as asthma (Currie *et al., J. Immunol.* 164:3878-3886 (2000); Suphioglu *et al., Lancet* 339:569 (1992)). Thus, macrophage C-type lectin receptor binds to and internalizes allergenic

particles initiating or promoting an inflammatory pathway common to airway inflammatory diseases such as asthma (see specification page 5, line 30 to page 6, line 2). Based on the homology to the mouse macrophage C-type lectin, SEQ ID NO: 4 is expected to bind antigens, such as allergenic particles; therefore, the utility of the polypeptide of SEQ ID NO: 4 is also substantial.

On page 4 of the Office Action dated 12/13/2002, the Examiner states that "the specification asserts that SEQ ID NO: 6 [the extracellular portion] is useful on its own as a soluble protein, but does not disclose that this use is teaching only that this can be confirmed by expression in mammalian cells and sequencing of the cleaved product." Applicants respectfully traverse for the following reasons. The polypeptide of SEQ ID NO: 6 has a specific and substantial utility because it can be used to attenuate the inflammatory response associated with allergic airway disease such as asthma. It is well known in the art that the soluble portion of a cell surface receptor can be used as an antagonist to block the function of the receptor by binding to ligands before the ligands can bind to the membrane-bound receptor (*i.e.* competitive inhibition), thereby inhibiting or reducing the activity of the receptor. It follows that in the case of the type II C-type lectin receptor SEQ ID NO: 4, the soluble portion (SEQ ID NO: 6) can bind antigens, such as allergenic particles, before they bind to and activate an inflammatory allergic response. Therefore, the polypeptide of SEQ ID NO: 6 could be used to attenuate the inflammatory response associated with diseases such as asthma. Indeed, scientists have shown that soluble lectins were able to suppress, in a dose dependent manner, allergen-stimulated bronchial inflammation associated with asthma (Wang *et al., Clin. Exp. Allergy* 31:652-662 (2001)). Thus the polypeptide of SEQ ID NO: 6 has a substantial utility that is also described in the specification at least on page 5, line 30 to page 6, line 2.

For the reasons discussed above, Applicants respectfully submit that the claimed invention has a utility that is credible, substantial and specific to the type II C-type lectin family of proteins. Applicants thus respectfully request withdrawal of the rejection under 35 U.S.C §101.

35 U.S.C. §112, First Paragraph Enablement Rejections Should be Withdrawn

The Claims are Enabled Since the Claimed Sequences have Utility

The rejection of Claims 10, 11, 20, and 31 under 35 U.S.C. §112, first paragraph for asserted lack of enablement because the invention lacked a specific and substantial or a well established utility should be withdrawn for the reasons discussed above with respect to utility.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance, and a Notice of Allowance is respectfully requested as soon as possible. If there are any questions regarding these amendments and remarks, or if further discussion would expedite allowance of the claims, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Date: 4 April, 2003

By: Renée S. Polizotto

Renée S. Polizotto, Ph.D.
Agent for Applicants
Registration No.: 53,474
NUVELO (formerly Hyseq, Inc.)
675 Almanor Avenue
Sunnyvale, CA 94085
(408) 215-4522
(408) 524-8145 (Telefacsimile)

HYS-5
Exhibit A


```
1    MVPE----------------------------------------  00002860Ff201_1
1    MTSEITYAEVRFKNEFKSSGINTASSAASK  gi5823974_DCIR

5    --EEPQDREKGLWWFQLKVWSMAVVSILLL  00002860Ff201_aa
31   ERTAPHKSNTG---FPKLLCASLLIFFLLL  gi5823974_DCIR

33   SVCFTVSSVVPHN-FMYSKTVKRLSKLREY  00002860Ff201 1
58   AISFFIAFVI-----FFQKYSQLLEKKTTK  gi5823974_DCIR

62   QQYHSSLTCVMEG---KDIED--WSCCPTP  00002860Ff201_1
83   ELVHTTLECVKKN---MPVEETAWSCCPKN  gi5823974_DCIR

87   WTSFQSSCYFISTGMQSWTKSQKNCSVMGA  00002860Ff201_1
110  WKSFSSNCYFISTESASWQDSEKDCARMEA  gi5823974_DCIR

117  DLVVINTTEEHDFIIHNLKRNSSYFLGLSH  00002860Ff201 1
140  HLLVINTQEEQDFIFQNLQEESAYFVGLSD  gi5823974_DCIR

147  PRGRRHWQWVDHTPYNENVTFWHSGEPNNL  00002860Ff201_1
170  PEGQRHWQWVDQTPYNESSTFWHPREPSDP  gi5823974_DCIR

177  D-ERCAIINFR-SSQEWGWNDIHCHVPHKS  00002860Ff201_1
200  N-ERCVVLNFRKSPKRWGWNDVNCLGPQRS  gi5823974_DCIR
          PS00615

205  ICEMKKIYIYMKYSPWKCVWVGIHRCRKLN  00002860Ff201_1
229  VCEMMKIHL                       gi5823974_DCIR
     PS00615
```

Decoration 'Decoration #1': Box residues that match 00002860Ff201_aa1 exactly.

KEY

Bold Residues = Lectin/crd PFAM signature (PF00059)

Underlined Residues = PROSITE domain for c-lectin (PS00615)

Markings Above the Alignment (J. Immunol. 1999, 163:1973-1983):
- Dots (.)= Calcium-binding residues.
- Asterisks (*) = Intramolecular Disulfide Cysteines
- +++ = Mannose/glucose regonition motif.
- Canonical c-lectin residues are indicated above their respective positions.